UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

FEDERAL TRADE COMMISSION and THE PEOPLE OF THE STATE OF NEW YORK, by LETITIA JAMES, Attorney General of the State of New York,

Plaintiffs,

v.

QUINCY BIOSCIENCE HOLDING COMPANY, INC., a corporation; QUINCY BIOSCIENCE, LLC, a limited liability company; PREVAGEN, INC., a corporation d/b/a/ SUGAR RIVER SUPPLEMENTS; QUINCY BIOSCIENCE MANUFACTURING, LLC, a limited liability company; and MARK UNDERWOOD, individually and as an officer of QUINCY BIOSCIENCE HOLDING COMPANY, INC., QUINCY BIOSCIENCE, LLC, and PREVAGEN, INC.,

Defendants.

Case No. 1:17-cv-00124-LLS

PLAINTIFFS' OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE PLAINTIFFS' EXPERTS

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Plaintiffs, the Federal Trade Commission, and the People of the State of New York, by Letitia James, Attorney General of the State of New York, respectfully submit this Opposition to Defendants' Motion to Exclude Plaintiffs' Experts (ECF No. 307). Defendants advance various meritless arguments in support of their motion to exclude testimony from Plaintiffs' experts, including claims that Plaintiffs' experts applied "the wrong legal standard" in assessing Defendants' purported substantiation for the challenged advertising claims, that Plaintiffs' experts lack the requisite qualifications to render their opinions, and that Plaintiffs' experts offer opinions that are both irrelevant and unreliable. Because Defendants' arguments are inconsistent with Federal Rules of Evidence 402, 403, and 702, and *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993), Plaintiffs request that the Court deny Defendants' Motion to Exclude Plaintiffs' Experts.

I. INTRODUCTION

This case is about Defendants' advertising claims that their product, Prevagen, improves memory and cognition and is clinically proven to do so. Plaintiffs contend that Defendants lack substantiation for these advertising claims and therefore have violated the FTC Act and New York consumer protection law. Each of Plaintiffs' experts offers opinions that are directly relevant to the key issue in this case – whether Defendants' advertising claims are substantiated. Dr. Mary Sano, an undisputed expert in the fields of memory, cognition, and clinical trials, and Dr. Janet Wittes, an undisputed expert in biostatistics and clinical trial design and implementation, explain why Defendants' clinical study – the Madison Memory Study – does not show that Prevagen improves memory or cognition. Dr. Peter Malaspina, an expert in economics, econometrics, and statistics, examined one of Defendants' re-analyses of the Madison Memory Study data and determined that the re-analysis was incorrectly conducted and that Defendants' conclusions regarding the re-analysis should be disregarded. Dr. Jeremy Mark

Berg, an expert in biochemistry, pharmacology, and physiology as it relates to metabolism, reviewed the relevant literature and data and concluded that there is no plausible theory as to how Prevagen could work. Each of Plaintiffs' experts offers a unique perspective on Defendants' purported substantiation for their advertising claims, and their testimony should be permitted.

Defendants first argue that the Court should exclude the opinions of Drs. Sano and Wittes because these experts applied "the wrong legal standard," utilizing instead their "own heightened" standard when reviewing Defendants' purported substantiation for Prevagen. According to Defendants, the legal standard applied by Drs. Sano and Wittes is appropriate for drugs and not for dietary supplements like Prevagen. Defendants argue that their opinions, therefore, do not "fit the case," are irrelevant, and would serve only to confuse the jury. Defendants argue as well that the opinions of Drs. Sano and Wittes regarding the *post hoc* nature of Defendants' subgroup data analyses are based entirely on speculation and are therefore unreliable.

Defendants' argument that Drs. Sano and Wittes applied "the wrong legal standard" is based on a wholly flawed understanding of the role that *scientific* experts play in helping courts determine the level of evidence necessary to support challenged advertising claims. Long-established case law provides that courts look to what experts in the relevant scientific fields would require to support the claims at issue. Here, as Plaintiffs are challenging Defendants' claims that (1) Prevagen improves memory and cognition; and (2) Defendants' randomized clinical trial ("RCT"), the Madison Memory Study, proves Prevagen's efficacy, the relevant scientific fields are memory, cognition, and clinical trials. Dr. Sano articulated the relevant

scientific standards of the fields and opined that evidence from an RCT in humans is required to establish Prevagen's efficacy for memory and other cognitive benefits.

Having properly opined on the requisite evidence to support the challenged claims, Dr. Sano applied the standards of her fields in assessing the Madison Memory Study and other substantiation materials. Dr. Sano found the Madison Memory Study to be fatally flawed and opined that Defendants' other materials were insufficient to support the challenged claims. Similarly, Dr. Wittes applied the standards of her fields and opined that the Madison Memory Study did not yield statistical significance. Drs. Sano and Wittes set out the standards in the relevant scientific fields and measured the extant substantiation against them, in accordance with the analytical framework long established in substantiation case law. Their opinions therefore are both entirely appropriate and wholly relevant.

Furthermore, Defendants are wrong that Drs. Sano and Wittes applied their "own heightened" standard that is inappropriate for assessing claims for dietary supplement products. Dr. Sano's opinion that the challenged claims need to be supported by a well-conducted RCT is consistent with well-established case law in which courts have looked to experts to determine the level of scientific support necessary to substantiate health claims, including claims for dietary supplement products. Moreover, her conclusions are consistent with case law requiring RCTs for such claims. In this case, an RCT is the appropriate standard for the additional reason that Defendants specifically have claimed in their advertisements that their RCT proved Prevagen's efficacy. Long-established case law and the FTC's industry guide, "Dietary Supplements: An Advertising Guide for Industry" ("FTC Guidance"), provides that Defendants were required to possess the level of substantiation claimed in their ads.

Finally, Defendants' argument that Drs. Sano's and Wittes's opinions regarding the *post hoc* nature of the subgroup analyses are entirely "speculative" takes their deposition testimony out of context and ignores completely the wide range of evidence these experts cite in their reports, and to which they testify in their depositions, in support of their opinions. While Defendants may believe that other evidence supports a different view of the Madison Memory Study's target population, they cannot credibly argue that the opinions of Drs. Sano and Wittes regarding the *post hoc* nature of the subgroups are without evidentiary basis. Defendants' argument that the opinions of Drs. Sano and Wittes regarding this issue should be excluded therefore is without merit.

Defendants next attack the qualifications and opinions of Peter A. Malaspina, Ph.D., Plaintiffs' expert in economics, econometrics, and statistics, whom Plaintiffs retained to assess the opinions proffered by Defendants' expert, Dr. David Katz, on yet another *post hoc* re-analysis of the Madison Memory Study. This re-analysis was performed in 2019 during the pendency of this litigation and approximately seven years after the Madison Memory Study was completed. It was purportedly done using an econometric model known as "Seemingly Unrelated Regressions" ("SUR") and was performed by Dr. Howard Beales and two economists employed by Georgetown Economic Services.[1]

Dr. Malaspina's assignment with respect to Dr. Beales's re-analysis was discrete – to determine whether Dr. Beales's re-analysis was properly programmed as a SUR model, and, if so, whether it yielded reliable statistical evidence to support Dr. Katz's opinions. If allowed to testify, Dr. Malaspina will establish that Dr. Beales programmed his purported SUR re-analysis

[1] Georgetown Economic Services is a subsidiary of Kelley Drye & Warren, the law firm that represents Corporate Defendants in the instant matter.

in such a way that it violates the assumptions of a SUR model – statistical errors that Dr. Malaspina was able to discern just by looking at the code Dr. Beales used to program his re-analysis. (The associated output provided by Defendants also further confirms the errors identified by Dr. Malaspina.) Moreover, when Dr. Malaspina corrected Dr. Beales's re-analysis to comply with the assumptions of a SUR model, the results were not statistically significant.[2] Since Dr. Malaspina's assignment concerns matters of economics, econometrics, and statistics, his advanced degrees and experience in these fields, as well as his years of experience using the statistical software at issue, more than qualify him to opine on these matters. Defendants' argument that Dr. Malaspina is not qualified to evaluate Dr. Beales's re-analysis is without merit.

Defendants' argument that Dr. Malaspina's analysis is unreliable because he conceded as much, or cherry-picked his analyses, is similarly meritless and reflects Defendants' misrepresentations of Dr. Malaspina's report, testimony, and analysis. As Dr. Malaspina made clear in both his report and testimony, his opinions about Dr. Beales's analysis were limited to assessing its reliability as statistical evidence, not authoring new analyses intended to make independent statistical inferences on the efficacy of Prevagen. Such an acknowledgment is not a concession by Dr. Malaspina that his own analysis is unreliable under any stretch of the imagination. Nor has Dr. Malaspina cherry-picked his analyses or withheld information that formed the basis of his opinions, as Defendants contend. In fact, Defendants have all the existing codes and resulting output that Dr. Malaspina considered in reaching his conclusions.

In addition, Dr. Malaspina's opinions on the Bonferroni correction (a statistical correction that would address the multiple outcomes and subgroups in the Madison Memory

[2] Notably, Defendants have not challenged Dr. Malaspina's central argument that Dr. Beales's re-analysis is not in fact a SUR analysis.

Study) should not be excluded. Dr. Malaspina has offered opinions to correct misstatements made by Dr. Katz that the SUR model and the Bonferroni correction are mutually exclusive, which follow directly from Dr. Katz's claim that a SUR analysis is more appropriate than a Bonferroni correction. As Dr. Malaspina explained, the claim that the Bonferroni correction and a SUR analysis are mutually exclusive is simply not true. To the extent that Defendants believe that other statisticians may disagree about the appropriateness of a Bonferroni correction, that is a matter that is suitable for cross-examination, not for exclusion of expert testimony.

Defendants also contend that Plaintiffs' expert, Dr. Jeremy Mark Berg, is unqualified and attack his testimony as irrelevant and unreliable. Dr. Berg is prepared to testify that apoaequorin, the primary ingredient in Prevagen, has no plausible mechanism of action – i.e., there is no reason to believe that it could work as advertised. Defendants have not advanced any viable argument as to how Dr. Berg is unqualified or how his testimony is unreliable. Defendants also have not explained why Dr. Berg's opinions are irrelevant to this action, in which an important element is whether Prevagen actually improves memory and cognition. Dr. Berg's straightforward testimony would help the jury understand a key issue in this case, and it should be permitted.

II. THE OPINIONS PROFFERED BY DRS. MARY SANO AND JANET WITTES ARE RELEVANT AND RELIABLE

Plaintiffs tasked Dr. Sano—an undisputed expert in the fields of memory, cognition, and clinical trials—to assess whether Defendants' substantiation, or any other materials, supported the claims that Prevagen improved memory or provided other cognitive benefits. Dr. Sano applied the standards of her fields of expertise and determined that an RCT is the requisite level of support for such claims. Dr. Sano then evaluated Defendants' RCT, as well as their other substantiation materials, against the relevant scientific standards and found all to be insufficient.

Plaintiffs asked Dr. Wittes, whose expertise in biostatistics (including the design and analysis of clinical trials) is not in dispute, to focus more narrowly on whether Defendants' RCT demonstrated any statistically significant benefit of Prevagen over placebo. Evaluating the RCT against the standards of her scientific field, she found that Defendants' RCT does not demonstrate any such benefit. As set forth below, the opinions of Drs. Sano and Wittes are relevant, reliable, and, in addition to the standards of the relevant scientific fields, based on Defendants' own documentary and testimonial evidence.

A. Drs. Sano and Wittes Applied the Correct Standards

Defendants' argument that the opinions of Drs. Sano and Wittes should be excluded because they applied "the wrong legal standard" fundamentally misunderstands the role of scientific experts in substantiation cases. Courts regularly look to experts in the relevant *scientific* fields to determine the evidence needed to support efficacy claims. *See, e.g.*, *Daniel Chapter One v. FTC*, 405 F. App'x 505, 506 (D.C. Cir. 2010) ("Nor is there anything unreasonable about the specific type of basis required by the Commission, namely, 'competent and reliable scientific evidence' including clinical trials with human subjects. … As noted in the [FTC Guidance], the Commission generally relies upon experts for evidence of the 'accepted norms in the relevant field,' and the expert testimony before the Commission in the present case supports the type of substantiation it required of [Daniel Chapter One].") (internal citation omitted) (denying review of an FTC order); *FTC v. Roca Labs, Inc.*, 345 F. Supp. 3d 1375, 1387 (M.D. Fla. 2018) (citing testimony of FTC expert that "[t]o prove a weight-loss claim, 'experts in the field of obesity treatment and weight loss would require well-designed and properly conducted clinical trials'"); *FTC v. COORGA Nutraceuticals Corp.*, 201 F. Supp. 3d 1300, 1309 (D. Wyo. 2016) (stating that "it is appropriate to consider the amount of substantiation required by the relevant scientific community in determining whether the advertiser's claim is false,

misleading, or unsubstantiated"); *FTC v. Alcoholism Cure Corp.*, No. 3:10-cv-266-J-34JTB, 2011 WL 13137951, at *27 (M.D. Fla. Sept. 16, 2011) ("'The Court can look to what experts in the relevant area of study would consider to be adequate in determining the amount of and type of evidence that is sufficient' for scientific validation of the claims.") (quoting *FTC v. Braswell*, No. CV 03–3700 DT (PJWX), 2005 WL 4227194, at *10 (C.D. Cal. Sept. 27, 2005)); *FTC v. Nat'l Urological Grp.*, 645 F. Supp. 2d 1167, 1202 (N.D. Ga. 2008). This approach also is set forth in the FTC Guidance, which states that a "guiding principle for determining the amount and type of evidence that will be sufficient is what experts in the relevant area of study would generally consider to be adequate." (Graham Decl. (ECF No. 308) Ex. A, FTC Guidance at QUI-FTCNY-00189213.)

In this case, Dr. Sano, whose expertise in the fields of memory, cognition, and clinical trials is unchallenged, applied the standards of the fields and determined that evidence from an RCT in humans is required to establish the efficacy of Prevagen for memory and other cognitive benefits. (Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 1-12, 23-29, 41.) Dr. Sano then evaluated Defendants' Madison Memory Study against the standards for a properly designed, conducted, and analyzed RCT and found it to be wholly insufficient to support the challenged claims. (*Id.* ¶¶ 23-107, 121-23; Graham Decl. (ECF No. 308) Ex. C, Sano Rebuttal Report ¶¶ 3-13.)[3] Similarly, Dr. Wittes, whose expertise in biostatistics—including the areas of clinical trial design, analysis, and data interpretation—is unchallenged, applied the standards of

[3] Furthermore, despite Defendants' contention to the contrary, Dr. Sano also addressed the sufficiency of Defendants' non-RCT evidence, including open-label, animal, and observational studies (as well as the arguments of Defendants' experts regarding such evidence) and determined that it, too, wholly failed to support the challenged claims. (Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 15-16, 29, 117-20; Graham Decl. (ECF No. 308) Ex. C, Sano Rebuttal Report ¶¶ 1-2, 3.e-f, 14-17, 19.)

those fields and found the Madison Memory Study to be fatally flawed in multiple respects, including that its results were not statistically significant. (Graham Decl. (ECF No. 308) Ex. F, Wittes Aff. Report ¶¶ 13-78; (Graham Decl. (ECF No. 308) Ex. G, Wittes Rebuttal Report ¶¶ 1-27; Wone Decl. Ex. B, Wittes Tr. 26:6—33:9.) The opinions of Drs. Sano and Wittes are properly based on the standards necessary to demonstrate efficacy in their fields of scientific and statistical expertise, and thus are wholly relevant and reliable.[4]

Defendants make much of the irrelevant fact that Drs. Sano and Wittes never reviewed the legal definition of "competent and reliable scientific evidence" as articulated in the FTC Guidance, a document published by the FTC to assist marketers in complying with federal law. Courts have found that marketers must possess "competent and reliable scientific evidence" to substantiate health-related efficacy claims. *See, e.g.*, *FTC v. NPB Adver., Inc.*, 218 F. Supp. 3d 1352, 1358 (M.D. Fla. 2016); *FTC v. Nat'l Urological Grp.*, 645 F. Supp. 2d 1167, 1202 (N.D. Ga. 2008); *FTC v. QT, Inc.*, 448 F. Supp. 2d 908, 961 (N.D. Ill. 2008). The FTC Guidance states that "competent and reliable scientific evidence" is "defined in FTC cases" as:

> [T]ests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results.

(Graham Decl. (ECF No. 308) Ex. A, FTC Guidance at QUI-FTCNY-00189212.) As Defendants correctly note, however, Drs. Sano and Wittes are not legal experts, nor are they

[4] By contrast, as articulated in Plaintiffs' *Daubert* motion, Defendants' experts never set forth the standards required in their purported fields of scientific expertise to support the claims at issue. For example, Dr. Schwartz, who has a Ph.D. in neuroscience, never discusses the standards particular to that field of science. Rather, Defendants' experts applied a standard based on their flawed interpretation of FTC law as expressed in the FTC Guidance and non-relevant FDA law. (Pls. MOL (ECF No. 304) 6-14.)

marketers seeking to comply with the law. They therefore have no reason or need to look to legal standards or documents explaining the law. In fact, it would have been entirely inappropriate for them to opine on the proper legal standard, attempt to explain the law, or offer an opinion on whether Defendants had complied with the law. *See United States v. Stewart*, 433 F.3d 273, 311 (2d Cir. 2006) ("[A]n opinion that purports to explain the law to the jury trespasses on the trial judge's exclusive territory."); *United States v. Duncan*, 42 F.3d 97, 101 (2d Cir. 1994); *United States v. Bilzerian*, 926 F.2d 1285, 1294 (2d Cir. 1991) ("Although an expert may opine on an issue of fact within the jury's province, he may not give testimony stating ultimate legal conclusions based on those facts."). Therefore, the fact that Drs. Sano and Wittes did not review the FTC Guidance—or were unfamiliar with case law, statutes, regulations, or legal definitions—is neither surprising nor of any legal import.

In any case, the analyses performed by Drs. Sano and Wittes are entirely consistent with prior case law and the FTC Guidance's definition of "competent and reliable scientific evidence." Although they might not have seen the definition of that term as spelled out in the FTC Guidance, Drs. Sano and Wittes in fact assessed whether the Madison Memory Study, as well as Defendants' other proffered studies, were "conducted and evaluated in an objective manner" with "procedures generally accepted in the[ir] profession to yield accurate and reliable results." Consequently, there is no "analytical gap" between the language of the FTC Guidance and the analyses performed by Drs. Sano and Wittes.

B. Drs. Sano and Wittes Did Not Create Their "Own," Heightened Standard

Furthermore, Defendants' argument that the jury would be confused by Drs. Sano and Wittes applying their "own," heightened standard in requiring an RCT and assessing the sufficiency of Defendants' proffered substantiation materials is without merit. As set forth above, Drs. Sano and Wittes properly based their opinions on the standards of the relevant

scientific fields of memory, cognition, clinical trials, and biostatistics. Defendants' argument that the requirement of a well-conducted RCT is somehow unique to Dr. Sano, constitutes a legal opinion, or is inappropriate for this case is wholly undermined by the numerous cases in which courts have looked to experts and held that marketers needed an RCT to substantiate efficacy claims, including those made for dietary supplement products. *See, e.g.*, *POM Wonderful v. FTC*, 777 F.3d 478, 505 (D.C. Cir. 2015); *Daniel Chapter One v. FTC*, 405 F. App'x 505, 506 (D.C. Cir. 2010) (noting that there was nothing "unreasonable about the specific type of basis required by the Commission, namely, 'competent and reliable scientific evidence' including clinical trials with human subjects"); *Roca Labs*, 345 F. Supp. 3d at 1381, 1387-89; *NPB Adver., Inc.*, 218 F. Supp. 3d at 1359; *COORGA Nutraceuticals*, 201 F. Supp. 3d at 1309 (finding that an RCT is the requisite level of substantiation); *Alcoholism Cure Corp.*, 2011 WL 13137951, at *39 (noting that many courts have "embrac[ed] the placebo-controlled, double-blind clinical study as the most basic and fundamental requirement for scientific validity and reliability to support health-related claims (including dietary supplements)"); *Nat'l Urological Grp., Inc.*, 645 F. Supp. 2d at 1202; *FTC v. Direct Mktg. Concepts, Inc.*, 569 F. Supp. 2d 285, 303-04 (D. Mass. 2008) (stating that it is "well-accepted that double-blind, placebo-controlled studies are necessary to substantiate health-related efficacy claims"); *FTC v. Braswell*, No. CV 03-3700, 2005 WL 4227194, at *10 (C.D. Cal. Sept. 27, 2005) (listing cases where "courts . . . have found or upheld that double-blind, placebo controlled studies are required to provide adequate substantiation for various efficacy claims, including claims for dietary supplements").

In this case, an RCT is the requisite level of substantiation for the additional reason that Defendants repeatedly have claimed in their advertising that Prevagen's efficacy was proven by such a study. (*See, e.g.,* Olson Decl. (ECF No. 224) ¶¶ 28-30, Ex. E at QUI-FTCNY-00013352);

Ducklow Decl. (ECF No. 260) Attachment 1, Prevagen.com at FTC-0000139.0003-04.) It is well-established that marketers are required to possess the specific level of substantiation claimed in their advertisements. *See, e.g.*, *Roca Labs, Inc.*, 345 F. Supp. 3d at 1388 (noting that an establishment claim is required to have the level of proof claimed in the ad); *Coorga Nutraceuticals*, 201 F. Supp. 3d 1300 at 1309 ("If an establishment claim 'states a specific type of substantiation,' the 'advertiser must possess the specific substantiation claimed.'" (quoting *Removatron Corp. v. FTC*, 884 F.2d 1489, 1492 n.3 (1st Cir. 1989)); *FTC v. Wellness Support Network*, No. 10-cv-04879-JCS, 2014 WL 644749, at *16 (N.D. Cal. Feb. 19, 2014) (finding that "for establishment claims advertisers must have the level of substantiation referenced in the claim itself" and applying this standard to advertising claims that referenced clinical and scientific studies); *Direct Mktg. Concepts, Inc.*, 569 F. Supp. 2d at 298-99.

Defendants cite the civil contempt case of *Basic Research, LLC v. FTC*, No. 2:09-cv-0779, 2014 WL 12596497 (D. Utah Nov. 25, 2014) in support of their argument that Drs. Sano and Wittes applied the "wrong" standard by opining that an RCT was needed to support Defendants' efficacy claims or when evaluating how the Madison Memory Study was conducted or analyzed. (Defs. MOL (ECF No. 307) at 9-10, 13.) In *Basic Research*, however, the court had to decide whether the FTC had established by clear and convincing evidence that defendants violated a specific provision of a prior court order that did not expressly mention RCTs. *Basic Research*, 2014 WL 12596497 at *1. In this case, the Court is not being asked to interpret a prior order or whether Defendants are violating its terms. Therefore, looking to the testimony of Drs. Sano and Wittes, whose expertise in the relevant fields of memory, cognition, clinical trials, and

biostatistics is unquestioned, to determine whether the claims are substantiated is both appropriate and supported by well-established case law.[5]

C. The Opinions of Drs. Sano and Wittes Regarding the *Post Hoc* Nature of Defendants' Subgroup Analyses Are Based on the Standards of the Relevant Scientific Fields and Defendants' Own Document and Testimonial Evidence

Defendants' argument that Drs. Sano's and Wittes's opinions regarding the *post hoc* nature of the subgroup analyses are based only on "speculation" takes their deposition testimony out of context and ignores completely the wide range of evidence the experts cite in their reports, and to which they testify in their depositions, in support of their opinions.[6]

Defendants cite to a partial answer of Dr. Sano in response to a question about language in one of the Madison Memory Study write-ups in an attempt to show that her opinion regarding the *post hoc* nature of the subgroup analyses was based entirely on her "own speculation." (*See* Defs. MOL (ECF No. 307) at 17.) For Dr. Wittes, Defendants cite to two passages in which she states that she did not know "when" the AD8 0-2 subgroup analysis was planned, the "date" that the AD8 0-2 analysis was conducted, or "the dates" on which Defendants conducted their

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[5] To the extent the Court finds *Basic Research* indistinguishable from the instant case, Plaintiffs respectfully submit that the reasoning of the *Basic Research* court is incorrect, as evidenced by the multitude of cases cited above holding that RCTs may be required to substantiate health claims for dietary supplement products.

[6] In the section of their brief challenging the factual bases of Drs. Sano and Wittes regarding the *post hoc* subgroup analyses, Defendants state more broadly that these experts' opinions regarding the Madison Memory Study's "design, methodology, and data analysis" are based on speculation and assumption. (Defs. MOL (ECF No. 307) at 16.) However, as Defendants address and request the exclusion of opinions relating only to the issue of the *post hoc* nature of the subgroup analyses, Plaintiffs here address only that issue. To the extent that Defendants attack the foundation of any other aspects of Drs. Sano and Wittes's criticisms of the Madison Memory Study, they have failed to cite any supporting evidence. Moreover, such additional attacks would be baseless, because, as detailed above and set forth in Drs. Sano's and Wittes's reports, Drs. Sano and Wittes based all criticisms of the Madison Memory Study on the standards of the field of clinical trial design, implementation, and analysis, as well as the documents they reviewed.

analyses at the end of the study. (*Id.* at 17-18.) Defendants, however, ignore completely the other deposition testimony of both Drs. Sano and Wittes, as well as the experts' reports, that fully set forth and explain the multitude of evidentiary bases on which these experts base their opinions.

As an initial matter, Drs. Sano and Wittes, applying the standards of their fields, opined that analyses of subgroups not prespecified in the study protocol are, *by definition*, *post hoc* in nature and are inherently unreliable. (Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 23-27, 34.a, 38, 57; Ex. F, Wittes Aff. Report ¶¶ 12, 33-35.) They explain that, unless researchers document at the outset of a trial all subgroups they intend to use to show efficacy, the researchers would be free to redefine the study population after seeing study data in order to claim findings of significance. (Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 38, 56-57; Ex. F, Wittes Aff. Report ¶¶ 34-35.) Therefore, analyses of such *post hoc* subgroups are inherently unreliable and cannot appropriately be used to support claims that an intervention is efficacious. (Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 38, 56-57; Ex. F, Wittes Aff. Report ¶¶ 33-35; Ex. G, Wittes Rebuttal Report ¶ 22.) Drs. Sano and Wittes opine that as the Madison Memory Study protocol did not specify any subgroups—and, in fact, included no reference to the AD8 scale whatsoever—the analyses of the AD8 0-1 and 0-2 subgroups are *post hoc* and do not support a finding that Prevagen improves memory or cognition. (Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 56-57, 68-69, 73, 78; Ex. F, Wittes Aff. Report ¶¶ 33-35, 54, 78.b-c; Ex. G, Wittes Rebuttal Report ¶ 22.)

Furthermore, in addition to the fact that the Madison Memory Study protocol listed no subgroups, Drs. Sano and Wittes cite a wide range of evidence to support their opinion that the AD8 0-1 and 0-2 subgroups were not the study's target population. That evidence includes: (1)

the multiple study write-ups and the deposition testimony of Kenneth Lerner, all of which referenced a study population of over 200 subjects, over twice the number of subjects in the two subgroups (Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 55-56, 72, 99; Ex. C, Sano Rebuttal Report ¶ 5);[7] (2) Defendants' interim press releases regarding the Madison Memory Study results, none of which referenced subgroups (Graham Decl. (ECF No. 308) Ex. F Wittes Aff. Report ¶ 61); (3) the fact that the inclusion criteria of the study's protocol do not correlate with persons with an AD8 score between 0 and 2 (Wone Decl. Ex. A, Sano Tr. 114:17—120:16, 121:24—122:9, 123:9—124:5: Ex. B, Wittes Tr. 80:2—82:13; Underwood Decl. (ECF No. 226) Ex. R, Madison Memory Study protocol at QUI-FTCNY-00068426); (4) the fact that the exclusion criteria of the study's protocol do not necessarily exclude persons with an AD8 score over 2 (Wone Decl. Ex. A, Sano Tr. 122:19—123:8; Underwood Decl. (ECF No. 226) Ex. R, Madison Memory Study protocol at QUI-FTCNY-00068426); (5) the fact that Defendants did not randomize study subjects by AD8 score, or group of scores (Graham Decl. (ECF No. 308) Ex. C Sano Rebuttal Report ¶ 5); (6) the fact that Defendants' list of subgroups included many subgroups of subjects scoring from 3 to 8 on the AD8 scale, in addition to those scoring from 0 to 2 (Graham Decl. (ECF No. 308) Ex. F Wittes Aff. Report ¶ 62); and (7) the fact that Defendants' 2011, 2014, and 2016 Madison Memory Study write-ups included results for

[7] Notably, Defendants have never explained the discrepancy between the entire study population and the number of subjects who made up the two subgroups, despite the fact that, as their own expert, Dr. Katz, acknowledged: "there is a legitimate question as to why the authors enrolled individuals with higher AD8 scores if the intended target population was individuals with minimal to no impairment." (Graham Decl. (ECF No. 225) Ex. O, Katz Aff. Report ¶ 56.b.) Dr. Sano rejected Dr. Katz's speculation regarding the possible reasoning, noting that, in her 30 plus years of experience, she had never seen "any instance in which persons conducting a study knowingly included subjects who were not part of the intended target population, let alone doubled the size of the subject group by doing so." (Graham Decl. (ECF No. 308) Ex. C, Sano Rebuttal Report ¶ 5.)

subjects with AD8 scores greater than 2, specifically subjects scoring from 2 to 5 on the AD8 scale. (Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 81, 97-98; Ex. F, Wittes Aff. Report ¶ 60.) As noted by Dr. Wittes in her report, "[i]t was not until the August 2016 Madison Memory Study Paper, dated approximately five years after the Study was completed, that the researchers focused exclusively on the AD8 0-1 and 0-2 subgroups." (Graham Decl. (ECF No. 308) Ex. F, Wittes Aff. Report ¶ 60; *see also* Graham Decl. (ECF No. 308) Ex. B, Sano Aff. Report ¶¶ 81, 97-98.)

While Defendants may point to other evidence that they believe supports a different view of the Madison Memory Study target population, they cannot credibly argue that the opinions of Drs. Sano and Wittes regarding the *post hoc* nature of the non-prespecified subgroups are "speculative" and without evidentiary basis. Defendants' criticisms of the factual bases of Drs. Sano and Wittes's opinions go to the weight, rather than the admissibility, of their testimony, and any perceived flaws in the factual foundation of the opinions are properly addressed through cross-examination. *Zerega Ave. Realty Corp. v. Hornbeck Offshore Transp., LLC*, 571 F.3d 206, 213-14 (2d Cir. 2009); *US Bank Nat'l Assoc. v. PHL Variable Life Ins. Co.*, 112 F. Supp. 3d 122, 134-35 (S.D.N.Y. 2015).[8] Defendants' argument that the opinions of Drs. Sano and Wittes regarding this issue should be excluded therefore is without merit.

III. DR. MALAPSINA IS QUALIFIED AND HIS OPINIONS ARE RELEVANT AND RELIABLE

Defendants challenge the qualifications of Plaintiffs' expert, Dr. Malaspina, and claim that his testimony is irrelevant and unreliable. (Defs. MOL (ECF No. 307) at 3-4, 28-34.)

[8] Similarly, if Defendants were to contend that there are discrepancies between Drs. Sano's and Wittes's reports and their deposition testimony regarding the *pro hoc* issue, those discrepancies would go to the weight of their testimony, not its admissibility. *FTC v. Qualcomm, Inc.*, No. 17-CV-00220-LHK, 2018 WL 6460573, at *5 (N.D. Cal. Dec. 10, 2018).

Defendants make the incredible argument that Dr. Malaspina, an expert in economics, econometrics, and statistics, lacks the qualifications to evaluate the opinions of Defendants' expert, Dr. David Katz, on one of the many *post hoc* re-analyses of the Madison Memory Study that was purportedly done using the SUR model.

It is ironic that Defendants question Dr. Malaspina's ample experience to analyze Defendants' purported SUR re-analysis when Dr. Katz, the only expert they have proffered to opine on this re-analysis, has no experience in econometrics generally, or in the SUR model specifically, and is merely parroting the opinions of Dr. Beales, one of the economists who performed the re-analysis. (*See* Pls. MOL (ECF No. 304) at 14-17.) Plaintiffs have moved to exclude Dr. Katz's testimony on this re-analysis due to his lack of qualifications. (*See id*.)

Should the Court deny Plaintiffs' requested relief, Dr. Malaspina is prepared to testify on rebuttal that Dr. Beales's re-analysis, is not, in fact, a SUR re-analysis and that when you correct Dr. Beales's re-analysis to comply with the assumptions of a SUR model, the results are not statistically significant. Given Dr. Malaspina's advanced degrees and experience in economics, econometrics, and statistics, as well as his extensive experience using the statistical software at issue, he is more than qualified him to opine on these matters.

Defendants' argument that Dr. Malaspina's analysis is unreliable because he conceded as much, or cherry-picked his analyses, are outright misrepresentations and should be rejected. In addition, Dr. Malaspina's opinions on the Bonferroni correction, which correct misstatements by Dr. Katz that the SUR model and the Bonferroni correction are mutually exclusive, should not be precluded because Defendants have failed to advance any valid basis for such preclusion.

A. Summary of Dr. Beales's Econometric and Statistical Errors as Identified by Dr. Malaspina

According to Drs. Katz and Beales, the SUR econometric model is a superior analytical technique for the Madison Memory Study given the likelihood that the study's nine outcome measures are correlated. (Graham Decl. (ECF No. 225) Ex. O, Katz Aff. Report ¶ 61; Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 11-13.) Yet, as Dr. Malaspina observes in his report, Dr. Beales generated an analysis that assumes that the study's nine outcome measures are uncorrelated, and, as a result of this flaw, the programmed analysis cannot be a SUR analysis. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 12, 31-32.)

In addition to failing to allow for correlation across the study's nine outcome measures, Dr. Beales's purported SUR analysis mistakenly assumed no correlation across a participant's repeated test scores over time, specifically at each of the study's five testing intervals on Days 0, 8, 30, 60, and 90. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 14, 31-32.) By erroneously programming his model in a way that ignored the correlations in a participant's test performance across the nine outcome measures and across the five testing intervals, Dr. Beales's programming treated the data as if there were vastly more individuals in the study than in actuality, and this error resulted in a re-analysis that was prone to erroneously finding a statistically significant effect from taking Prevagen (compared to a placebo) when there was no such effect. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶ 16.) Put differently, Dr. Beales's re-analysis treated the 45 test results for a single individual (9 outcome measures x 5 testing intervals) as if they were the test results taken from 45 different individuals. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶ 16.) Dr. Beales's errors in

programming his analysis are statistical and econometric in nature, and do not relate to flaws in epidemiology or clinical trials.

In analyzing Dr. Beales's re-analysis, Dr. Malaspina engaged in a two-step process. First, Dr. Malaspina reviewed the code programmed by Dr. Beales and the associated output provided by Defendants. Upon review of the code, Dr. Malaspina realized that it assumed that the Madison Memory Study's outcome measures, and each participant's performance over time, were uncorrelated in violation of the assumptions of a SUR model. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 12-14, 31-38.) The output from Dr. Beales's re-analysis also provided independent confirmation that Dr. Beales's re-analysis was programmed in such a way that it violated the assumptions of a SUR model. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 31-38, n.43.) Thus, Dr. Malaspina was able to conclude that Dr. Beales's re-analysis was not a SUR analysis just from a facial analysis of the code used by Dr. Beales and its associated output. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 31-38, n.43.)

Second, Dr. Malaspina corrected Dr. Beales's purported SUR analysis with one goal in mind: to use the model described by Dr. Beales in such a way that it accounted for the correlations it claimed to address. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 39-42, Exs. 4.1-4.2.) To do this, Dr. Malaspina used the bootstrapping method. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶ 41.) When Dr. Malaspina corrected Dr. Beales's fundamental programming errors – by keeping Dr. Beales's model specification but changing his code to allow for the correlation that Dr. Beales purportedly accounted for – Dr. Malaspina's correction showed that, according to Dr. Beales's own hypothesis test, the results provided no evidence that Prevagen has a statistically significant

effect when compared to a placebo. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 39-42.)

B. Dr. Malaspina is Qualified to Offer His Opinions on Defendants' Unreliable, *Post Hoc* Statistical Re-Analysis of the Madison Memory Study

In support of their motion to exclude Dr. Malaspina's testimony, Defendants point out that Dr. Malaspina purportedly lacks experience in fields of expertise irrelevant to SUR – clinical trials and epidemiology – and ignore the fact that Dr. Malaspina possesses ample experience in the relevant fields of expertise – economics, econometrics, and statistics generally, and with the SUR model specifically. (Defs. MOL (ECF No. 307) at 28-30.) With respect to Dr. Beales's re-analysis, Dr. Malaspina's assignment was straightforward: to determine whether the econometric model used by Dr. Beales was properly programmed as a SUR model, and if so, yielded reliable statistical evidence to support Dr. Katz's opinions. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 5-17.)

"Courts within the Second Circuit have liberally construed expert qualification requirements." *In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 412 (S.D.N.Y. 2016) (internal quotation marks omitted). Qualification of an expert "may be based on a broad range of knowledge, skills, and training." *Id.* (internal quotation marks omitted). Dr. Malaspina easily clears this bar.

His undergraduate and graduate studies in economics and econometrics, as well as his years of experience working in these fields, and prior professional experience using the SUR model, are more than sufficient to establish that he is a qualified expert in economics and econometrics and can evaluate and opine on Defendants' purported SUR re-analysis. Indeed, Defendants themselves concede that "Dr. Malaspina is a specialist in 'microeconomics, industrial organization, and econometrics.'" (Defs. MOL (ECF No. 307) at 26.) It is

unnecessary for Dr. Malaspina to be qualified in "analyzing clinical trial data" or in epidemiology, as Defendants' contend, because Plaintiffs retained him neither to render an opinion on the design or implementation of the Madison Memory Study nor to express an opinion about Prevagen's purported clinical efficacy. Moreover, the errors identified by Dr. Malaspina are fundamental errors related to econometrics and statistics, independent of the underlying data – the purported SUR analysis is not a SUR, and the underlying data have no bearing on this fact.

In reality, Dr. Malaspina's education and experience as an economist and econometrician, as well as his extensive familiarity with, and use of, the statistical software used by Dr. Beales to conduct the purported SUR re-analysis, provide him with the requisite knowledge needed to help the jury understand the flaws of Dr. Beales's econometric re-analysis, such that those flaws render the analysis unequivocally not a SUR analysis, and by extension unreliable.

1. Dr. Malaspina Is Qualified in the Relevant Fields of Economics and Econometrics.

Dr. Malaspina received a B.A. Double Major in Math and Economics from Vassar College and a Ph.D. in Economics with minors in Econometrics, Microeconomics, Law and Economics, and Industrial Organization from the University of North Carolina at Chapel Hill. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report Ex. 1.) In the field of econometrics specifically, Dr. Malaspina took multiple undergraduate and graduate courses in economics, econometrics, and statistics. (Wone Decl. Ex. C, Malaspina Tr. 16:7-24; 17:11—19:4.)

Not only does Dr. Malaspina hold advanced degrees in economics and econometrics, but he also has amassed significant practical experience in these fields during his career. After

completing his graduate studies, Dr. Malaspina worked for over ten years in positions that involve developing econometric models and conducting econometric analyses. (Wone Decl. Ex. C, Malaspina Tr. 19:17—20:13, 23:10—28:7, 33:15—34:9.) Dr. Malaspina also worked at the New York Attorney General's Office as a Chief Economist offering guidance to the Attorney General on a variety of matters.[9] (Wone Decl. Ex. C, Malaspina Tr. 28:16—31:24.)

2. Dr. Malaspina Has Extensive Experience Using the Relevant Statistical Software.

In addition to misrepresenting his relevant fields of expertise, Defendants also mischaracterize Dr. Malaspina's experience using the statistical tools necessary to evaluate Dr. Beales's re-analysis of the Madison Memory Study. Contrary to Defendants' assertions, Dr. Malaspina has ample experience with the SAS System, the statistical software that Dr. Beales used to run his purported SUR re-analysis and that Dr. Malaspina initially used to re-create Dr. Beales's re-analysis. As Dr. Malaspina testified, he has used the SAS System "[a] lot" during his time at Quantitative Economic Solutions, which has a best practice of using the SAS System when working with large data sets. (Wone Decl. Ex. C, Malaspina Tr. 34:18—36:11.)

Defendants next erroneously argue that Dr. Malaspina has no experience using a specific instruction in the SAS System known as "proc mixed statement" and contend that Dr. Malaspina only learned about this instruction by reading the SAS manual. The "proc mixed statement" is not a "technology," "program," or "system" as Defendants would have the Court believe. *See* (Defs. MOL (ECF No. 307) at 29-30.) Instead, users operate the SAS System by writing instructions in a computer programming language known as the SAS language. *See SAS Inst., Inc. v. World Programming Ltd*., 874 F.3d 370, 375 (4th Cir. 2017). The "proc mixed statement"

[9] As counsel for the New York Attorney General's Office noted during Dr. Malaspina's deposition, Dr. Malaspina "did not work on Quincy matters while he was at the AG." (Wone Decl. Ex. C, Malaspina Tr. 173:12-15.)

is an example of one of the many instructions that are part of the SAS computer programming language.

Contrary to Defendants' assertions, Dr. Malaspina did not testify that he had failed to use the proc mixed statement prior to this litigation. Instead, he explained that he was "not sure if [he'd] used it before the present matter[.]" However, he had "used several things like [the proc mixed statement] and it's possible that [he] used it at some point. . . ." Ultimately, however, Dr. Malaspina noted, "It's hard to remember every single instance where I've used SAS." (Wone Decl. Ex. C, Malaspina Tr. 54:13-20.)

In any event, even assuming that Dr. Malaspina had never previously used the proc mixed statement, this fact alone does not disqualify him as an expert. As an experienced economist well versed in using the SAS System, and its many different permutations of programming instructions, Dr. Malaspina certainly understands the theory and utility behind the proc mixed statement and has used other instructions like the proc mixed statement.

Nor should the fact that Dr. Malaspina reviewed the SAS System's user guide when evaluating Dr. Beales's re-analysis serve as a basis to disqualify him, as Defendants argue. In fact, Dr. Malaspina is ready to testify that it is common practice, and indeed a best practice, for users of the SAS System to refer to the guide, which is often revised (there are currently 15 versions), is thousands of pages long, and covers numerous programming instructions. In fact, the excerpt of the SAS System user guide that Dr. Malaspina reviewed and cited in his report covers one chapter that starts at page 6,048 and ends at page 6,234. (*See* Wone Decl. Ex. D, Excerpt of SAS/STAT 14.1 User's Guide The MIXED Procedure at NYAG-QUINCY-0003047.)

C. Dr. Malaspina's Opinions Regarding Defendants' SUR Analysis Are Reliable and Will Assist the Trier of Fact

Defendants next advance three meritless arguments to support their view that Dr. Malaspina's correction to Dr. Beales's so-called SUR re-analysis is unreliable and should be excluded. (Defs. MOL (ECF No. 307) at 30-39.) First, they contend that Dr. Malaspina himself admitted that his correction was not "suitable for drawing reliable conclusions about the available data," and then they argue that his correction was cherry-picked from numerous analyses that he ran on the data. Both arguments grossly misconstrue Dr. Malaspina's report, testimony, and analysis and should be rejected. Finally, Defendants' argument that Dr. Malaspina applied a correction to Dr. Beales' SUR re-analysis that is different from what Dr. Beales applied overlooks the fact that the correction was necessary to conform Dr. Beales's re-analysis to its stated description.

1. Dr. Malaspina Has Not Conceded That His Analysis Is Unreliable.

Dr. Malaspina's report contains a footnote that Defendants have taken out of context to advance a supposed admission by Dr. Malaspina that his correction to Dr. Beales's faulty analysis was unreliable. That footnote states,

> My corrections to Dr. Beales are intended to demonstrate that his analysis and reported results are unreliable. I am not opining that my corrections are sufficient to fully recover Dr. Beales' analysis such that it is suitable for drawing reliable conclusions about the available data.

(Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report n.15.)

As Dr. Malaspina explained at his deposition,

> So, when it comes to my opinions about the model, it's really about what did Dr. Beales say he was trying to do, and how did [Dr. Beales] describe what he did. And so, I'm just trying to demonstrate that what [Dr. Beales] actually did, in his analysis that he presented, wasn't that. So, I'm not saying that this is the right or wrong way to

> conduct an analysis of the underlying data, merely correcting what the – serious mistakes made by Dr. Beales.

(Wone Decl. Ex. C, Malaspina Tr. 67:18—68:3.)

Dr. Malaspina testified that he is not opining on whether the SUR model is appropriate for the Madison Memory Study or on whether his correction to Dr. Beales's analysis makes Dr. Beales's analysis suitable for drawing reliable conclusions; this is not equivalent to a concession by Dr. Malaspina that his own analysis is unreliable.

2. Dr. Malaspina Did Not Cherry-Pick Analyses to Include in His Report.

Defendants' next accusation – that Dr. Malaspina cherry-picked analyses to include in his report and failed to disclose evidence that was highly relevant to his conclusions – also rings hollow. Defendants have the raw data of the Madison Memory Study and the code used by Dr. Beales. In addition, Dr. Malaspina's report contains a complete statement of his opinions and the bases for them, as well as the materials he considered in forming his opinions. Defendants also were provided copies of Dr. Malaspina's supporting materials, which include code and native excel files that were used to generate the analyses described in his report. Dr. Malaspina's report describes his opinion that Dr. Beales did not perform a SUR analysis, a conclusion Dr. Malaspina was able to draw just from looking at Dr. Beales's code. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 31-38, n.43.) Dr. Malaspina's report and supporting materials disclose Dr. Beales's programming errors, the code Dr. Malaspina used to conform Dr. Beales's analysis to the SUR analysis described by Dr. Beales, and the resulting output. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 39-42, Ex. 3.1-3.2, 4.1-4.2.) In short, Dr. Malaspina's report contains all information that he considered and that was relevant to his conclusions.

In order to try to conform Dr. Beales's analysis to the SUR model described by Dr. Beales, Dr. Malaspina attempted to run Dr. Beales's program code in the SAS System with a modification, specifically an unstructured variance matrix, but the program "couldn't find a solution. It basically hung up. . . [which is a] technical issue . . . [where SAS is] trying to find a solution and it can't . . . ." (Wone Decl. Ex. C, Malaspina Tr. 90:20—91:21.) Consequently, the SAS System did not generate any output for Dr. Malaspina to analyze. Dr. Malaspina did not, and could not, consider output that simply does not exist.

Dr. Malaspina also testified that he used tools, like a pivot table in Excel, to facilitate his review of the output from his analyses. Specifically, Dr. Malaspina testified,

> [A]s you're programming this stuff up and trying to make sure that your, you know, results are correct, you may run small permutations of stuff just to see what's going on with the data. Stuff like that. Things that weren't – obviously weren't essential to my opinions things like looking at the data in summary form. So like, actually literally just pulling all the data into – I may have started in Excel, but just like looking at a pivot table and what does the stuff even look like. Those are important steps for just getting yourself comfortable and knowing what you're working with. But again, it's – this is sort of preliminary and – and not essential for the ultimate opinion.

(Wone Decl. Ex. C, Malaspina Tr. 92:24—93:21.) Dr. Malaspina's use of Excel, for instance, to facilitate his review of the output of his analyses simply changed the presentation of the data and is not a separate analysis that he considered in forming his opinions.

Exclusion of Dr. Malaspina's opinions is not warranted because Plaintiffs have produced the facts and data considered by Dr. Malaspina in forming his opinions. Defendants fail to explain how non-existent output or an Excel pivot table of the same analyses that were produced would be relevant to Dr. Malaspina's conclusions. They also fail to proffer any explanation for the supposed prejudice they have suffered from Dr. Malaspina's purported non-disclosure, nor

can they. *See Atkins v. County of Orange*, 372 F. Supp. 2d 377, 396 (S.D.N.Y. 2005) (citing *Softel, Inc. v. Dragon Med. & Scientific Comm., Inc.*, 118 F.3d 955, 961 (2d. Cir. 1997)). At Dr. Malaspina's deposition, Defendants had every opportunity to question Dr. Malaspina about his methodology, and Dr. Malaspina provided extensive detail about the methodology he used, first to re-create Dr. Beales's analysis, and then to correct the analysis.

For these reasons, the Court should reject Defendants' unfounded charge that Plaintiffs have withheld highly relevant evidence relating to Dr. Malaspina.

3. Dr. Malaspina's Application of the Bootstrapping Technique Was Necessary to Perform the Analysis Dr. Beales Described but Failed to Execute.

As Dr. Malaspina noted throughout his report, "Dr. Beales describ[ed] a SUR model framework in the Beales Paper, but he fail[ed] to actually use SUR due to errors in his program." (*See, e.g.*, Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶ 41.) Dr. Malaspina's "correction to Dr. Beales' analyses uses the same model specification provided in the Beales Paper but using SUR . . . ." (*Id.*) "Further, to address the possible correlations" in each participant's test performance across the Madison Memory Study's nine outcome measures and across the five testing intervals, Dr. Malaspina "implement[ed] the bootstrap method with the option for clustering over individual participants. Without this correction, Dr. Beales' analysis will effectively treat each individual's five days of test results the same as it would a single day of test results from five individuals." (*Id.*)

At his deposition, Defendants suggested that Dr. Malaspina's application of the bootstrap method was the "only reason [Dr. Malaspina's] model finds no statistical significance," but as Dr. Malaspina explained,

> [T]he reason why – my corrections to Dr. Beales produces different results is because it's – doing what he said he was doing and what he failed to program, so that has to do in part with the way you model

> – you allow the model to account for correlation across equations and also across – within individuals.

(Wone Decl. Ex. C, Malaspina Tr. 128:3-16.) Defendants thereafter asked Dr. Malaspina whether Dr. Beales had used the bootstrap method in his model, to which Dr. Malaspina responded, "[Dr. Beales] talks about random effects, and then does not use them, and so the bootstrap method is one way to incorporate the random effects." (Wone Decl. Ex. C, Malaspina Tr. 128:17-24.)[10] Testimony that explains the flaws in Dr. Beales's analysis, and the results that the analysis would yield if it had conformed to Dr. Beales's stated description, is certainly relevant and will assist the jury in evaluating whether Dr. Beales's purported SUR analysis, on its own or in combination with Defendants' other research, constitutes competent and reliable scientific evidence to substantiate Defendants' advertising claims. *See Amorgianos v. Amtrak*, 303 F.3d 256, 265 (2d. Cir. 2002) ("In fulfilling this gatekeeping role, the trial court should look to the standards of Rule 401 in analyzing whether proffered expert testimony is relevant, i.e., whether it 'has any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence.'") (internal quotations omitted).

D. Dr. Malaspina's Opinions Regarding the Bonferroni Correction Are Reliable and Will Assist the Trier of Fact

The last attack Defendants lodge against Dr. Malaspina relates to his opinion that Dr. Katz erroneously suggested in his report that a SUR analysis and a statistical correction known

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[10] Dr. Malaspina's testimony echoed the opinions he expressed in his rebuttal report wherein he wrote, "The Beales Paper also purports to include random effects (*see* Beales Paper, p. 4); however, due to errors in the Beales Program, these random effects are omitted, and thus the results reported in the Beales Paper are generated under the assumption that there is no correlation in test performances over time (within individuals) or across the different types of tests (see Section III.2 below)." (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶ 14, n.13; *see also id.* ¶ 35, n.44.)

as the Bonferroni correction are mutually exclusive. Specifically, in his report, Dr. Katz opined, "[t]he 'seemingly unrelated regression' approach is a more appropriate method to deal with related measures, as opposed to the Bonferroni correction." (Graham Decl. (ECF No. 222) Ex. O, Katz Aff. Report ¶ 61.) Dr. Malaspina countered that "[a] SUR analysis is perfectly compatible with the Bonferroni correction," and explained the foundation for his opinion. (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 17, 43-44.) According to Dr. Malaspina, "the Bonferroni correction is available as an option that can be used with the SUR analysis in standard statistical analysis software widely used by economists and econometricians such as STATA." (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶¶ 17, 43.) Furthermore, "[t]he Bonferroni correction option is also available in the Mixed Model procedure for the SAS software used by Dr. Beales . . . ." (Graham Decl. (ECF No. 308) Ex. L, Malaspina Rebuttal Report ¶ 43 n.59.) There was no need for Dr. Malaspina to apply a Bonferroni correction to his analysis because his assignment focused on whether Dr. Beales's analysis conformed to the assumptions of a SUR model, and whether the results of the analysis were statistically significant, which they were not. When Plaintiffs confronted Dr. Katz at his deposition about his suggestion that the SUR analysis and a Bonferroni correction are mutually exclusive, Dr. Katz responded, "No, not within the context of the given study. No, rather the opposite. It's my impression they do very different things" and he "certainly could imagine a study that would warrant something like a SUR analysis and a Bonferroni." (Wone Decl. Ex. E, Katz Tr. 211:12-24.)

Despite the apparent agreement between Drs. Malaspina and Katz on the compatibility of a SUR analysis and the Bonferroni correction, Defendants argue that the Court should exclude Dr. Malaspina's opinion because an article cited by Dr. Malaspina states that the use of the

Bonferroni correction is subject to "vociferous[]" arguments, and that "[t]o say that statisticians disagree on this would be indulging in understatement." (Defs. MOL (ECF No. 307) at 33.) The fact that other statisticians may disagree with Drs. Malaspina (and even it would appear, Dr. Katz) is not a basis for excluding Dr. Malaspina's opinion that use of the SUR model fails to obviate the need for a Bonferroni correction. To the extent that Defendants believe that Dr. Malaspina's opinion rests on "shaky grounds," the appropriate course of action for them would be "vigorous cross-examination" and "presentation of contrary evidence." *EEOC v. Mavis Disc. Tire, Inc*., 129 F. Supp. 3d 90, 115 (S.D.N.Y. 2015) (quoting *Daubert v. Merrell Dow Pharms. Inc.*, 509 U.S. 579, 596 (1993)); *see also Amorgianos v. Amtrak*, 303 F.3d 256, 267 (2d. Cir. 2002) (noting "our adversary system provides the necessary tools for challenging reliable, albeit debatable, expert testimony.)

IV. DR. BERG IS QUALIFIED AND HIS OPINIONS ARE RELEVANT AND RELIABLE

Defendants also contend that Plaintiffs' expert, Dr. Berg, is unqualified, and attack his testimony as irrelevant and unreliable. (Defs. MOL at 3, 19-26.) Dr. Berg is prepared to testify that apoaequorin, the primary ingredient in Prevagen, has no plausible mechanism of action. As Dr. Berg explains, apoaequorin is a protein and, like other typical proteins, it is expected to degrade into amino acids, and possibly small peptides, in the stomach and small intestine. It can therefore have no more effect on memory or cognition than any other typical protein. Defendants have not advanced any viable argument as to how Dr. Berg is unqualified or how his testimony is unreliable. Dr. Berg's opinions are also clearly relevant to this action, in which an important element is whether Prevagen actually improves memory and cognition.

A. Dr. Berg's Qualifications and Opinions

Dr. Berg is a chemist, biochemist, and biophysicist who has published more than 120 peer-reviewed scientific publications, half of which involved proteins, and several of which included studies of protein degradation, including within organisms. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 3.) He is an author of three major textbooks, including *Biochemistry*, which has been one of the most widely used biochemistry textbooks throughout the world. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 4.) Plaintiffs retained Dr. Berg to testify regarding possible mechanisms of action for Prevagen – i.e., ways in which it could have a therapeutic effect on the human body. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 7.) Dr. Berg concluded that apoaequorin, orally consumed, would not be expected to have any therapeutic effect on the human body. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report. ¶¶ 14, 55.) This conclusion was based on his knowledge about how compounds that share apoaequorin's characteristics would behave when orally consumed, as well as Defendants' own research showing that apoaequorin is rapidly digested like other typical proteins. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 15-21.)

Dr. Berg also evaluated the multiple theories Defendants have advanced as possible mechanisms by which Prevagen might have an effect on the human body – including the effects on memory and cognition claimed by Defendants for Prevagen. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 7, 47-50; Graham Decl. (ECF No. 308) Ex. J, Berg Rebuttal Report ¶¶ 16-26, 29-33.) Because these other mechanism of action theories are entirely speculative and in no way tied to evidence specific to apoaequorin, Plaintiffs are seeking to preclude such testimony. (*See* Pls. MOL (ECF No. 304) at 28, 30-47.) If, however, the Court allows Defendants to present such speculative and irrelevant testimony, Dr. Berg intends to opine on why these purported mechanisms are speculative, implausible, and irrelevant to apoaequorin.

The parties, and their experts, agree that a mechanism of action for Prevagen is not known. They also agree that apoaequorin is a protein. Based on apoaequorin's characteristics, Dr. Berg has also concluded that (a) there is no plausible mechanism of action for Prevagen and (b) there is no evidence of any specific mechanism of action for Prevagen.[11] Dr. Berg bases this conclusion on his extensive background and expertise in the relevant scientific fields. He need not be an expert on memory or cognition to reach the conclusion that apoaequorin would behave in the body like any typical protein when orally consumed. Dr. Berg examined the minimal evidence that Defendants have presented on apoaequorin and concluded that "all available experimental evidence is consistent with the concept of rapid degradation, and no evidence has been presented that refutes it." (Graham Decl. (ECF No. 308) Ex. J, Berg Rebuttal Report ¶ 34.)

Dr. Berg first considered Defendants' original theory about how Prevagen works to improve memory and cognition – by crossing into the bloodstream, crossing the blood-brain barrier into the brain, and binding calcium in the brain. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 15-21, 31.) He notes that typical proteins, unlike other compounds, have characteristics that – when orally consumed – prevent them from entering into the bloodstream and further prevent them from entering into the brain. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 17-21.) Typical proteins, Dr. Berg concludes, are broken down into their

[11] Defendants' attempt to summarize Dr. Berg's expert reports gets it wrong. Dr. Berg did not say that "an orally administered protein cannot have a specific biological effect in the brain." (*Compare* Defs. MOL (ECF No. 307) at 19 *with* Graham Dec. Ex. I, Berg Aff. Report ¶¶ 10-11.) Dr. Berg also did not summarily conclude that apoaequorin could not cross the blood-brain barrier; rather, he noted that Defendants' evidence demonstrates that apoaequorin could not cross the blood-brain barrier. (*Compare* Defs. MOL (ECF No. 307) at 19 *with* Graham Decl. Ex. I, Berg Aff. Report ¶ 12.) Defendants also assert that Dr. Berg "only 'briefly considered some alternative possible mechanisms by which Prevagen might have a therapeutic effect,'" but they only cite Dr. Berg's affirmative report, and not his rebuttal report responding to Defendants' experts' theories, or his deposition testimony explaining why certain of those theories were not meritorious. (Defs. MOL (ECF No. 307) at 19.)

constituent parts – amino acids and perhaps small peptides – before reaching the bloodstream, and thus would not have the same effects on the body as the intact proteins from which they came. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 20.)

Next, Dr. Berg applied his background knowledge to evidence Defendants have presented about apoaequorin specifically; such evidence only confirms Dr. Berg's conclusion that apoaequorin would behave like a typical protein. Specifically, Defendants' *in vitro*, dog, and rat studies on apoaequorin together support Dr. Berg's conclusion that apoaequorin would be broken into amino acids and possibly small peptides in the stomach, and further broken down in the small intestine. Dr. Berg examined an *in vitro* study of apoaequorin in a simulated gastric fluid which showed that apoaequorin would not survive the conditions of the stomach. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 25-27.) Dr. Berg also examined experimental results presented by Defendants that purportedly showed that apoaequorin crossed the blood-brain barrier in dogs and exerted a protective effect in the brains of rats. Using his knowledge of biochemistry and general principles of experimental design and interpretation, Dr. Berg analyzed the experimental results and determined that Defendants' conclusions regarding their study results were flawed and that the studies did not, in fact, show that orally administered apoaequorin can reach the brain. (S*ee* Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 25-29, 36-46.)

Having refuted Defendants' original theory that apoaequorin has a direct effect on human brain cells through calcium-binding, and having addressed the significance of Defendants' own *in vitro* and animal research, Dr. Berg next addressed other possible theories about how Prevagen might work. He concluded, based on his ample education, training, and experience in the fields

of biochemistry, chemistry, and biophysics, as well as protein digestion, that no viable mechanism of action has been advanced.

B. Dr. Berg Is Qualified to Offer His Opinions

Defendants erroneously argue that Dr. Berg's testimony requires expertise in memory, cognition, and digestion, and that Dr. Berg admits that he has no expertise in any of these areas. (Defs. MOL (ECF No. 307) at 20-22.) Defendants have not, however, properly identified the fields of expertise that are relevant to Dr. Berg's testimony. One does not need to be an expert in memory, cognition, or digestion in order to offer the opinions Dr. Berg is offering in this case. Dr. Berg is an expert in the relevant fields of biochemistry, pharmacology, and physiology as it relates to metabolism, including protein metabolism (an aspect of digestion). He therefore possesses the requisite scientific knowledge about the behavior of substances, particularly proteins, as they enter the body orally, encounter stomach acids and digestive enzymes, and do or do not get absorbed into the bloodstream. (*See* Wone Decl. Ex. F, Berg Tr. at 48:17—49:19.)

Defendants state that Dr. Berg is "admittedly not an expert in human digestion" (Defs. MOL (ECF No. 307) at 3), but they ignore that Dr. Berg is an expert on the aspects of digestion that are relevant to his testimony. Apoaequorin is a typical protein and what happens to such proteins when they are orally consumed falls squarely within Dr. Berg's expertise. Dr. Berg confirmed that he is an expert on the general characteristics of digestion (Wone Decl. Ex. F, Berg Tr. at 53:9-11) and that he has conducted studies related to protein digestion (Wone Decl. Ex. F, Berg Tr. at 23:21—24:16). Indeed, one of Dr. Berg's textbooks includes extensive discussion of protein digestion. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report. ¶ 4.) The same book also includes a chapter on drug development that discusses drug distribution, including the role of the blood-brain barrier and the difficulties of using proteins as orally-delivered drugs. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report. ¶ 4.) Dr. Berg is also

more than qualified to discuss the results of Defendants' analyses and tests related to apoaequorin, due to his expertise in experimental methods, designs, and interpretations of data related to orally delivered proteins. (*See, e.g.*, Wone Decl. Ex. F, Berg Tr. at 63:22—65:10 (discussing methods of determining degradation products of proteins and experience in such methods); Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report Ex. A (curriculum vitae) (detailing education, training, publications, and journal experience in experimental methods, designs, and interpretations of data related to orally delivered proteins).)

Defendants err in arguing that Dr. Berg needs to be an expert in memory or cognition in order to offer his opinions as to Prevagen's purported effects. (Defs. MOL (ECF No. 307) at 20-22.) Dr. Berg relies on his extensive body of knowledge to opine, well within his field, on the characteristics of apoaequorin, and why those characteristics make it unlikely that apoaequorin – a protein that is digested like other dietary proteins – could have *any* effect on the human body (other than a minor nutritional one derived from its amino acids). Dr. Berg does not need to be an expert on memory or cognition in order to draw that conclusion. As Dr. Berg notes, apoaequorin would be expected to degrade into amino acids and possibly small peptides in the digestive system – and all of the available evidence regarding apoaequorin confirms Dr. Berg's conclusion. (*See* Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 15-46; Graham Decl. (ECF No. 308) Ex. J, Berg Rebuttal Report ¶¶ 3-22.) Dr. Berg properly concludes that there is no evidence that apoaequorin could reach an area of the body where it could have an effect; no evidence that peptides from apoaequorin survive digestion; and no evidence that peptides or amino acids derived from apoaequorin could have an effect. (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 51-55; Graham Decl. (ECF No. 308) Ex. J, Berg Rebuttal Report ¶¶ 34-

36.) This conclusion is one that is easily drawn by an expert in biochemistry and aspects of pharmacology and digestion.

The cases cited by Defendants are inapposite. In *LVL XIII Brands, Inc. v. Louis Vuitton Malletier S.A.*, the witness opined on an issue requiring expertise in empirical analyses, but had no training or experience in such analyses. 209 F. Supp. 3d 612, 639-40 (S.D.N.Y. 2016) (cited in Defs. MOL (ECF No. 307) at 21). In *In re Rezulin Prod. Liab. Litig.* 309 F. Supp. 2d 531, 549 (S.D.N.Y. 2004), and *In re Mirena IUD Prod. Liab. Litig.*, 169 F. Supp. 3d 396, 477 (S.D.N.Y. 2016), the experts admitted they were not experts in the relevant field. Dr. Berg, by contrast, identified relevant fields as "biochemistry, physiology, pharmacology" and has not disavowed expertise in those areas. (Wone Decl. Ex. F, Berg Tr. at 37:21—38:4.) Defendants do not dispute that Dr. Berg is a biochemist. Dr. Berg is also an expert in the relevant aspect of physiology as it relates to metabolism and in pharmacology as it relates to mechanisms of drug actions and pharmacogenomics. (Wone Decl. Ex. F, Berg Tr. at 38:18—39:22.)

C. Dr. Berg's Testimony Regarding Potential Mechanisms of Action for Prevagen Is Reliable and Has Foundation

Defendants' next argument, that Dr. Berg should be precluded from testifying because of his purported failure to consider all possible mechanisms of action for Prevagen, also lacks merit. (Defs. MOL (ECF No. 307) at 23, 25.) The fact is that Dr. Berg reviewed all available evidence regarding apoaequorin's biological characteristics, including Defendants' own evidence, and concluded that the evidence shows that apoaequorin could not have an effect on the human body if taken orally. There was no need to venture further – a plausible mechanism of action for Prevagen is not known.[12] Dr. Berg was not required to consider every possible mechanism

[12] Contrary to Defendants' assertion, Dr. Berg never stated that a mechanism of action *need* be known in order for a compound to have a clinical effect. (*See* Defs. MOL (ECF No. 307) at 3,

because the characteristics of apoaequorin, and the available evidence connected to it, point to the only reasonable conclusion about what happens when it is orally consumed: it breaks down in the stomach and small intestine like other dietary proteins.

In any event, to the extent that the Court credits Defendants' arguments that Dr. Berg failed to consider every possible mechanism of action for Prevagen, that does not warrant exclusion of his testimony. In *In re Fosamax Prods. Liab. Litig.*, this court considered an argument that an expert failed to consider all the possible data related to her opinions that there was no known or proven causal relationship between a drug and a medical condition, and that the mechanism of action by which such a relationship could exist was uncertain. 645 F. Supp. 2d 164, 206 (S.D.N.Y. 2009). The plaintiffs argued that because the expert did not consider all possible data, her opinion "relied on an incomplete and biased factual foundation" and should therefore be excluded. *Id.* at 207. The court rejected that argument, noting that this issue was "proper subject for cross-examination but do[es] not warrant exclusion." *Id.* at 208.

Even though it was not required, Dr. Berg did consider other speculative theories advanced by Defendants and concluded they were not viable. (*See* Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶¶ 47-50; Berg Rebuttal Report ¶¶ 16-26, 29-33.) The theories that Defendants claim Dr. Berg did not address were ones advanced for the first time in the improper rebuttal report of Dr. David Gortler. (*See, e.g.*, Matuschak Decl. (ECF No. 305) Ex. I, Gortler Rebuttal Report ¶ 41 (discussing, among other things, new theories based on active transport, a pharmacological signaling cascade, and prodrugs).) Dr. Berg cannot be faulted for failing to

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23.) The citations to Dr. Berg's testimony on this point confirm that Dr. Berg does not dispute that notion. (*See* Defs. MOL (ECF No. 307) at 23 (and deposition testimony cited therein).) Because Dr. Berg does not advance this conclusion, there is no "'analytical gap' between the data referenced and the opinion rendered," as Defendants assert. (Defs. MOL (ECF No. 307) at 23.)

consider mechanism of action theories that were presented by Defendants for the very first time in an improper rebuttal report – especially where such theories are so untenable in the context of Prevagen and apoaequorin. As Dr. Berg noted, there is no reason to believe that apoaequorin, or products from it, would be actively transported; would cause a pharmacological signaling cascade; or would behave as a prodrug, as Dr. Gortler speculates. (Wone Decl. Ex. F, Berg Tr. at 87:19—90:5.)

The only specific purported omission identified by Defendants was their theory that "apoaequorin could react with receptors either in the stomach or elsewhere in the mucus membranes of the gastrointestinal tract." (Defs. MOL (ECF No. 307) at 25.) Dr. Berg did not testify that he did not consider this theory. Instead, he testified that there was no reason to believe this theory to be viable:

> Q. Did you consider whether apoaequorin could react with receptors either in the stomach or elsewhere in the mucus membranes of the GI tract?
>
> A. In principle, but there's, again, no biological reason that those receptors should be present for a protein that has no homolog in anything that we would normally come in contact with.

(Wone Decl. Ex. F, Berg Tr. at 88:2-9.)

The cases cited by Defendants on this issue are inapposite. Defendants cite In *In re Mirena Prod. Liab. Litig.*, 169 F. Supp. 3d 396 (S.D.N.Y. 2016), for the proposition that Dr. Berg's purported "failure to give reasonable explanations for discounting or dismissing . . . "alternative possibilities" warrants exclusion of his testimony. (Defs. MOL (ECF No. 307) at 26.) In that case, the expert was presented with reasonable alternative explanations for his conclusion but could not adequately explain why he dismissed them. *Id.* at 435-36. Defendants also cite *Dependable Sales & Serv. v. TrueCar, Inc.*, 311 F. Supp. 3d 653 (S.D.N.Y. 2018), for

the proposition that "expert testimony was unreliable since it failed to eliminate alternative competing explanations." (Defs. MOL (ECF No. 307) at 26.) In that case, a damages expert failed to support his own conclusions with the available data and made an unsupported assumption about the plaintiff's sales markets. 311 F. Supp. 3d at 662-63. By contrast, in this case, Dr. Berg has provided reasonable explanations for discounting Defendants' mechanism of action theories. (*See, e.g.*, Graham Decl. (ECF No. 308) Ex. J, Berg Rebuttal Report ¶¶ 16-18 (noting that the field of orally presented bioactive peptides is controversial, that the proteins cited by Defendants' expert Dr. Goodman have different digestion characteristics from apoaequorin, and that no peptides resulting from apoaequorin have been shown to exist); *id.* ¶ 27 (observing that regulation of calcium levels in the brain has no basis as a mechanism of action theory because there is no evidence that apoaequorin can cross the blood-brain barrier); *id.* ¶¶ 29-33 (concluding that Defendants' experts' gut-brain axis theories have not been shown to have relevance to apoaequorin); Wone Decl. Ex. F Berg. Tr. at 88:2-9 (testifying that there is no biological reason that apoaequorin would react with receptors in the stomach or gastrointestinal tract); *id. a*t 89:23 – 90:5 (noting that he knows of no examples in which prodrugs are amino acids or peptides, which are the digestion products of apoaequorin).)

Defendants also argue that Dr. Berg's conclusions regarding other potential mechanisms of action lacked foundation because he purportedly failed to consider every possible mechanism of action – including mechanisms Defendants have not even proposed. (Defs. MOL (ECF No. 307) at 25-26.) Defendants take issue with Dr. Berg's very straightforward conclusion that he "ha[s] not seen evidence in the literature or otherwise that apoaequorin could have *any* therapeutic effect on the body through *any other* mechanism of action." (Defs. MOL (ECF No. 307) at 25 (quoting Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 55) (emphasis

supplied by Defendants).) Notably, Defendants do not argue that there *is* such evidence, because they cannot. Their experts' speculative theories do not have evidence tied to apoaequorin, or apoaequorin's characteristics, that would make any of their theories viable. Dr. Berg made that clear in his expert reports and at his deposition. (*See, e.g.*, Graham Decl. Ex. I, Berg Aff. Report ¶¶ 48-50; Graham Decl. Ex. J, Berg Rebuttal Report ¶¶ 16-26, 29-33; Wone Decl. Ex. F, Berg Tr. at 88:2—90:5.)

D. Dr. Berg's Testimony Regarding the Gut-Brain Axis Theory Is Reliable and Has Foundation

Defendants argue that Dr. Berg's testimony also lacks foundation because he supposedly conceded the viability of one of Defendants' multiple speculative theories – that Prevagen might work via the gut-brain axis. (Defs. MOL (ECF No. 307) at 24-26.) Defendants' experts have presented a vague theory that Prevagen might have some effect on the brain via the "gut-brain axis," which is a theory that changes in the gut microbiome can have some effect on the brain. (*See* Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 50.) Specifically, because it is clear that orally-consumed apoaequorin is broken down in digestion and cannot have an effect on the body, Defendants alternatively theorize that apoaequorin affects the brain through communication between the brain and the stomach. (*See* Graham Decl. (ECF No. 308) Ex. J, Berg Rebuttal Report ¶¶ 29-33 (discussing the gut-brain axis theories advanced by Defendants' experts).) This theory is speculative, not tied to Prevagen or apoaequorin, and Defendants' experts should not be allowed to opine on it. (*See* Pls. MOL (ECF No. 304) at 35-36, 42-47.) If the Court should allow Defendants' experts to speculate about the gut-brain axis theory, Dr. Berg should be allowed to explain why the theory that Prevagen might function via the gut-brain axis has no merit.

Defendants argue that Dr. Berg "conceded" that the gut-brain axis is a plausible mechanism of action or, alternatively, that Dr. Berg's conclusions regarding the gut-brain axis are outside his expertise and/or based on insufficient data. (Defs.' MOL (ECF No. 307) at 3, 22-25.) As Defendants acknowledge, Dr. Berg's conclusion regarding the gut-brain axis theory is that it was *not* a plausible mechanism of action for Prevagen. (Defs.' MOL (ECF No. 307) at 24.) Defendants apparently base their contention that Dr. Berg made the opposite alleged concession on the fact that a journal on which Dr. Berg served as the editor-in-chief published articles regarding the gut-brain axis. (Defs. MOL (ECF No. 307) at 25.) The fact that a journal publishes articles on the gut-brain axis theory does not mean that theory applies to Prevagen. Defendants do not, and cannot, cite any such article addressing the gut-brain axis as a viable mechanism of action theory for *Prevagen* (or apoaequorin).

Defendants are correct that Dr. Berg considers gut-brain axis theories to be "a topic of current research interest." (*See* Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 50.) Indeed, Dr. Berg cited and considered multiple references that discuss suggestions of a relationship between the gut microbiome and the brain. (*See* Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 50; Graham Decl. (ECF No. 308) Ex. J, Berg Rebuttal Report ¶ 30.) Importantly, however, Dr. Berg made clear that the gut-brain axis is not a plausible mechanism of action for Prevagen. He based this conclusion on the fact that "[t]here is no evidence, and no reason to believe, that apoaequorin at the doses used [in Prevagen] would have any effect on the gut microbiome, particularly in light of the ample evidence that [it] is completely or almost completely broken down before it leaves the stomach." (Graham Decl. (ECF No. 308) Ex. J, Berg Aff. Report ¶ 50.)

Defendants also seem to argue that Dr. Berg failed to base his gut-brain axis opinions on adequate data. (Defs. MOL (ECF No. 307) at 24.) They argue that Dr. Berg "summarily dismisses the gut-brain axis as a potential mechanism of action for Prevagen as 'not plausible,' without citing a single basis or methodology in support." (Defs. MOL (ECF No. 307) at 24.) This argument fails to acknowledge that Dr. Berg considered observations made in mice studies (Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 50); observations of powerful antibiotics that dramatically change the makeup of the gut microbiome (*id.*); the evidence that orally consumed apoaequorin is broken down before it leaves the stomach (*id.*); multiple recent studies suggesting possible influences of the gut microbiome on mood and cognition (Berg Rebuttal Report ¶ 31); and the reasoning and references relied upon by Defendants' purported experts regarding the gut-brain axis theory (*id.* ¶¶ 29, 31-33). Defendants' claim that Dr. Berg "fail[ed] to cite any foundation for his conclusions regarding the 'gut-brain axis'" is disingenuous at best. (Defs. MOL (ECF No. 307) at 24.)

Finally, it is unclear whether Defendants are challenging Dr. Berg's expertise to opine on the gut-brain axis. They do state that "Dr. Berg admitted at his deposition that he was not an expert on the gut-brain axis" (Defs. MOL (ECF No. 307) at 24) but the cited testimony does not say anything of the sort. Indeed, as Defendants note, a journal on which Dr. Berg served as editor-in-chief published multiple articles on the gut-brain axis during his tenure there. (Defs. MOL (ECF No. 307) at 25.) Moreover, Dr. Berg confirmed at his deposition that he has knowledge of this theory, including through seminars at the University of Pittsburgh School of Medicine (where he is a professor), Johns Hopkins University School of Medicine (where he was a professor and Director of the Department of Biophysics and Physical Chemistry), and probably at the National Institutes of Health (where he was Director of the National Institute for General

Medicine Sciences). (*See* Wone Decl. Ex. F, Berg Tr. at 85:2-7; Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 2.)

E. Dr. Berg's Testimony is Relevant

Defendants also appear to attack Dr. Berg's testimony as irrelevant, noting that a "definitively known" or "fully elucidated" mechanism of action is not required for clinical efficacy of dietary supplements. (Defs. MOL (ECF No. 307) at 3.) They also appear to argue that Dr. Berg's testimony is irrelevant because he did not consider or apply the "competent and reliable scientific evidence" standard required for substantiation of Defendants' advertising claims. (Defs. MOL (ECF No. 307) at 2-3.) Beyond these conclusory statements in the introduction of their Memorandum, Defendants do not elaborate on these points. Perhaps this is because they know that their first point is undisputed, and their second point has nothing to do with Dr. Berg's proposed testimony.

Dr. Berg was not asked to opine on requirements for dietary supplements or even whether Defendants' advertising claims were substantiated. His role was limited strictly to evaluating Defendants' claims about how Prevagen might work. (*See* Graham Decl. (ECF No. 308) Ex. I, Berg Aff. Report ¶ 7 ("I was asked to opine on the theory that the protein in Prevagen survives digestion and crosses the blood-brain barrier in order to have a therapeutic effect."); *id.* ("I was also asked to opine on other possible mechanisms by which Prevagen could have an effect.").) Having been presented with the various mechanism of action theories advanced by Defendants, Dr. Berg offered the straightforward expert opinion that (a) general principles of protein digestion, as well as Defendants' own evidence, refute Defendants' original mechanism of action theory and (b) Defendants' newest theories are purely speculative and unsupported by evidence. (*See* Graham Decl. (ECF No. 308) Ex. J, Berg Rebuttal Report ¶¶ 34-35.) The FTC Guidance upon which Defendants extensively rely makes clear a known mechanism of action can add

weight to evidence of claim substantiation. (Graham Decl. (ECF No. 308) Ex. A, FTC Guidance at QUI-FTCNY-00189213.) The only testimony Dr. Berg intends to offer is that there is no plausible mechanism of action for Prevagen, which is relevant to the key issue in this case – whether Defendants' advertising claims are substantiated.

V. CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that the Court deny Defendants' motion to exclude Plaintiffs' experts.

Respectfully submitted,

Dated: October 3, 2022

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CERTIFICATE OF SERVICE

I certify that on this 3rd day of October 2022, I caused service of the foregoing Plaintiffs' Opposition to Defendants' Motion to Exclude Plaintiffs' Experts to be made by electronic filing with the Clerk of the Court using the CM/ECF system, which will send a Notice of Electronic Filing to all counsel of record.

Dated: October 3, 2022

/s/ Annette Soberats
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